PATENT

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Dec. 10, 2002 — Joanne Bourguignon
Date — Joanne Bourguignon

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Robert Gellibolian
Application No.	:	09/932,728
Filed	:	August 17, 2001
For	:	METHOD AND SYSTEM FOR ARRAY SIGNAL GENERATION AND AMPLIFICATION

Examiner	:	Betty J. Forman
Art Unit	:	1634
Docket No.	:	10010543-1
Date	:	December 10, 2002

Box Non-Fee Amendment
Commissioner for Patents
Washington, DC 20231

AMENDMENT

Dear Sir:

In response to the Office Action dated September 10, 2002, please amend the application as follows:

In the Claims:

Please amend claim 16, as follows:

16. (amended) A method for covalently binding layers of partially double-stranded oligonucleotide linkers onto a double-stranded polynucleotide-target/polynucleotide-

probe pair bound to an array to form a complex that can be detected by analysis, the method comprising:

covalently binding an initial partially double-stranded oligonucleotide linker to the polynucleotide-target/polynucleotide-probe pair, the initial partially double-stranded oligonucleotide linker having at least two single-stranded oligonucleotide arms and forming a complex with at least two single-stranded arms; and

repeatedly

covalently binding a layer of one or more next partially double-stranded oligonucleotide linkers to the complex following association of the single-stranded oligonucleotide arms of the complex to complementary single-stranded arms of the next partially double-stranded oligonucleotide linkers, each one or more next double-stranded oligonucleotide linkers having a single-stranded oligonucleotide arm complementary to the one or more of the single-stranded oligonucleotide arms of the complex and at least one single-stranded oligonucleotide arm not complementary to the single-stranded oligonucleotide arms of the complex and not complementary to the single-stranded oligonucleotide arms of the one or more next double-stranded oligonucleotide linkers.

REMARKS

Claims 16-21 are currently pending in the application. In an Office Action dated September 10, 2002 ("Office Action"), the Examiner objected to claim 16, rejected claims 16-21 under 35 U.S.C § 112, second paragraph, rejected claims 16 and 19-21 under 35 U.S.C. § 102(e) as being anticipated by Goldberg et al., U.S. Patent No. 6,203,989 B1 ("Goldberg"), rejected claims 16 and 19-21 under 35 U.S.C. § 102(e) as being anticipated by Nilsen, U.S. Patent No. 6,274,723 B1 ("Nilsen"), and rejected claims 17-18 under 35 U.S.C. § 103(a) as being unpatentable over Goldberg in view of Urdea et al., U.S. Patent No. 5,124,246 ("Urdea"). Applicant's representative has endeavored to correct the problems identified by the Examiner in the objection and 35 U.S.C § 112 rejections. Applicant's representative respectfully traverses the 35 U.S.C. § 102(e) and 35 U.S.C. § 103(a) rejections, for reasons detailed below.

Both Goldberg and Nilsen disclose rather complicated procedures and chemical components, and neither particularly well illustrates the method and chemical components in figures. However, despite these deficiencies, it is quite clear to Applicant's representative that neither Goldberg nor Nilsen discloses methods related to Applicant's claimed method.

In Claim 16, Applicant claims:

> 16. A method for covalently binding layers of partially double-stranded oligonucleotide linkers onto a double-stranded polynucleotide-target/polynucleotide-probe pair bound to an array to form a complex that can be detected by analysis, the method comprising:
>
> covalently binding an initial partially double-stranded oligonucleotide linker to the polynucleotide-target/polynucleotide-probe pair, the initial partially double-stranded oligonucleotide linker having at least two single-stranded oligonucleotide arms and forming a complex with at least two single-stranded arms; and
>
> repeatedly
>
> covalently binding a layer of one or more next partially double-stranded oligonucleotide linkers to the complex following association of the single-stranded oligonucleotide arms of the complex to complementary single-stranded arms of the next partially double-stranded oligonucleotide linkers, each one or more next double-stranded oligonucleotide linkers having a single-stranded oligonucleotide arm complementary to the one or more of the single-stranded oligonucleotide arms of the complex and at least one single-stranded oligonucleotide arm not complementary to

the single-stranded oligonucleotide arms of the complex and not complementary to the single-stranded oligonucleotide arms of the one or more next double-stranded oligonucleotide linkers.

The claimed steps are illustrated in detail in Figures 10-20 of the Current Application. As shown in Figure 10, Applicant starts with a microarray to which single-stranded probe oligonucleotides are bound, and exposes the microarray to a sample solution containing target oligonucleotides. For probes complementary to subsequences of target molecules, hybridization occurs, forming double-stranded target/probe pairs, as, for example, the pair labeled 808 and 812 in Figure 10. Then, the probe is extended via primer extension, as shown in Figure 11, or the target is degraded via exonuclease, as shown in Figure 12, to create a double-stranded polynucleotide-target/polynucleotide-probe pair bound to the microarray, as clearly claimed above in the second underlined portion of claim 16. Next, as shown in Figure 15, an initial partially double-stranded oligonucleotide linker is bound to the polynucleotide-target/polynucleotide-probe pair, as clearly claimed above in the third underlined portion of claim 16. This step selects only double-stranded polynucleotide-target/polynucleotide-probe pairs for binding to the initial partially double-stranded oligonucleotide linker, thus initiating amplification of only those microarray features to which target molecules are bound.

Applicant's representative has read and reread Goldberg, Nilsen, and Urdea, and has failed to find anywhere in these cited references a teaching or suggestion of the method claimed in claim 16 for binding an initial linker to a double-stranded polynucleotide-target/polynucleotide-probe pair, nor of any structure or intermediate similar to the initial linker bound to a double-stranded polynucleotide-target/polynucleotide-probe pair, as shown clearly in Figure 15. In the cited portion of Golberg, for example, Goldberg discloses creation of a DNA matrix that includes two different types of partially double stranded polynucleotides, each with both ends having single stranded arms, that join together to form a matrix with at least one exposed, single-stranded arm. (Column 7, lines 4-32) *This single stranded arm then binds to a single-stranded target molecule*, and the resulting hybrid may be covalently cross-linked. (Column 7, lines 33-40) Various more complex conglomerations of target molecules and matrix molecules are then further described, including conglomerations that include antibodies and small-molecule ligands to which the antibodies bind, such as

biotin. What is not described in Goldberg is anything resembling the initial linker bound to a double-stranded polynucleotide-target/polynucleotide-probe pair, shown clearly in Figure 15 of the Current Application. There is simply no teaching or suggestion in Goldberg to covalently bind a partially double-stranded linker to a double-stranded polynucleotide-target/polynucleotide-probe pair.

The cited portions of Nilsen, which reference Figure 6 of Nilsen, are seemingly irrelevant to Applicant's claimed method. Nilsen discloses a method for using several single-stranded polynucleotides with predetermined sequences to assemble a dendrimer. Nilsen teaches or suggests absolutely nothing related to using dendrimeric complexes for amplifying a target/probe pair on a microarray substrate, nor any method specifically related to that of claim 16, where a partially double-stranded oligonucleotide linker is covalently bound to a double-stranded polynucleotide-target/polynucleotide-probe pair.

Thus, Applicant's representative can see no possible grounds for 35 U.S.C. § 102(e) anticipation rejections based on Goldberg or Nilsen. They simply do not disclose a method similar to that claimed in claim 16. Moreover, neither reference teaches or suggests binding an initial linker to a double-stranded polynucleotide-target/polynucleotide-probe pair that is "bound to an array," as clearly claimed in claim 16.

With regard to the 35 U.S.C. § 103(a) rejection based on Goldberg and Urdea, Applicant's representative is somewhat puzzled. As previously discussed, Goldberg does not teach Applicant's claimed method. In the cited sections of Urdea, Urdea discloses covalent linking of multimers using cross-linking agents (Column 8, line 67 – Column 9, line 30) and discloses enzymatically or chemically splicing together "two or more bifurcated multimers, 'comb-like' multimers or combinations thereof" (Column 12, lines 30-40). Urdea prepares multimers "by cloning (if linear), enzymatic assembly, chemical cross-linking techniques, direct chemical sysnthesis or a combination thereof." (Column 9, lines 33-35). Again, Urdea's multimers are seemingly unrelated to Applicant's double-stranded polynucleotide-target/polynucleotide-probe pair, which is clearly a hybridization and post-hybridization-processing product of single-stranded probe molecules and target molecules in a solution to which the probes are exposed. That is the meaning of the terms "target" and "probe," clearly defined in the specification on lines 16-29 of page 4 of the Current Application. A double-

stranded polynucleotide-target/polynucleotide-probe pair, as claimed in claim 1 and illustrated in Figure 15 of the Current Application, is not cross linked by Applicant's method, nor is it a "bifurcated multimers, 'comb-like' multimer, or combinations thereof." Applicant's representative can see no possible combination of Goldberg and Urdea that approaches the method of claim 16.

In summary, Applicant's representative can find no teaching or suggestion of the step of covalently binding an initial partially double-stranded oligonucleotide linker to a polynucleotide-target/polynucleotide-probe pair bound to an array, as clearly claimed in claim 16. This step represents the initiation of double-stranded-polynucleotide-target/polynucleotide-probe-pair amplification, without which specific target-binding features of a microarray would not be selectively amplified.

Based upon the above remarks, Applicant's representative respectfully requests reconsideration of the application and its early allowance.

Respectfully submitted,

Robert Gellibolian

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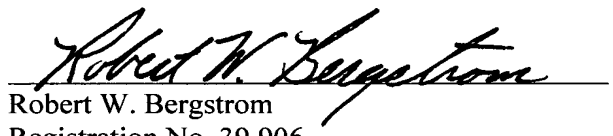

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